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LI, QIAN JANICE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,747	BLAU ET AL.	
	Examiner	Art Unit	
	Q. JANICE LI, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/12/08*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,8-13,19-21,34 and 39-45* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 46-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13,19-21,34 and 39-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment, and remarks filed 9/12/08 are acknowledged. Claims 1, 4-7, 14-18, 22-33, 35-38, 40 have been canceled. Claims 19-21, 34 have been amended.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 9/18/08 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

Applicant's election with traverse of species drawn to G-CSF as the mobilizing agent, NGF as the neuronal factor, and treating neurodegenerative disorders, now narrowed to a Purkinje neuron associated disorder is acknowledged.

The newly amended claims are directed to a method of treating disorders caused by Purkinje neuron cell deficiency. As such, it appears none of the diseases listed in claim 2 falls into this category as defined by the specification (paragraph 0105). Moreover, claim 3 excludes a lysosomal or peroxisomal disorder, which is known to have significant loss of Purkinje neurons in the nerve system. Accordingly, claims 2 and 3 no longer read on the elected species, and hence withdrawn from consideration.

Claims 8-13, 19-21, 34, 39, 41-45 are under current examination.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/993,045, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, the parent application is completely silent on Purkinje neurons and the Purkinje/bone marrow-derived heterokaryon. Accordingly, the priority date for instantly claimed subject matter has been established as the filing date of instant application, i.e. 10/16/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-13, 19-21, 34, 39, 41-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim (34) recitation "*a disorder caused by a deficiency of Purkinje neurons*". The specification defines the disorder by example:

> Purkinje cells play vital roles in maintaining balance and regulating movement. A loss of Purkinje cells results in deficits in these functions in several disorders: ataxia-telangiectasia, the most common cause of progressive ataxia in infancy; Menkes' Kinky Hair syndrome; the alcoholic cerebellar degenerations, particularly Wernicke-Korsakoff syndrome; and various prion diseases including scrapie, Creutzfeldt-Jakob, and Kuru.

However, the examples listed above are non-limiting. It is unclear what other disorders are caused by a deficiency of Purkinje neurons and embraced by the claims, and thus the metes and bounds of the claims are uncertain.

For the purpose of a compact prosecution, any disorder seeing the loss of Purkinje neurons, or affecting cerebellar contex where the Purkinje neurons are located will be considered as a disorder embraced by the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-13, 19-21, 34, 39, 41-45 stand rejected under 35U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to teach **an agent** that mobilizes bone marrow cells also "**induces**" formation of the Purkinje/bone marrow-derived heterokaryon in the nervous system of the individual as now claimed. The subject matter is now considered to be new matter, for reasons of record and following.

In the remarks, the applicant cited two paragraphs of the specification, and asserts the claims do not constitute new matter because the specification as-filed teaches bone marrow transplants and bone marrow cell mobilization therapies are two ways of increasing the number of bone marrow cells, which in turn promotes the formation of heterokaryons between bone marrow derived cells and Purkinje neurons.

The argument has been fully considered but found not persuasive because the argument missed the point and fails to address the issue of new matter. The instant new matter rejection was not on whether the specification discloses the two ways of increasing the number of bone marrow cells, but rather on the claimed **agent** capable of **inducing** the formation of the Purkinje/bone marrow-derived heterokaryon in the nervous system of the individual, the specification only teaches agents that **mobilize** bone marrow cells. The specification is completely silent on any agent that is capable of inducing formation of the Purkinje/BM-derived heterokaryon as now claimed. Thus, the amendment is a departure from or an addition to the disclosure of the application as filed. Accordingly, it introduces new matter into the disclosure.

Note the function of **increasing** the number of bone marrow cells in the circulation **differs** from that of **inducing** the formation of the Purkinje/bone marrow-derived heterokaryon in the nervous system of the individual. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "APPLICANT MUST CONVEY WITH REASONABLE CLARITY TO THOSE SKILLED IN THE ART THAT, AS OF THE FILING DATE SOUGHT, HE OR SHE WAS IN POSSESSION OF THE INVENTION. **THE INVENTION IS, FOR PURPOSES OF THE 'WRITTEN DESCRIPTION' INQUIRY, WHATEVER IS NOW CLAIMED.**" (See page 1117.) The specification does not "CLEARLY ALLOW PERSONS OF ORDINARY SKILL IN THE ART TO RECOGNIZE THAT [HE OR SHE] INVENTED WHAT IS CLAIMED." (See *Vas-Cath* at page 1116).

Claims 8-13, 19-21, 34, 39, 41-45 are newly rejected under 35U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed. The original disclosure fails to teach "a disorder *caused* by a deficiency of Purkinje neurons". The subject matter is now considered to be new matter, for reasons following.

The amended claim 34 recites "a disorder caused by a deficiency of Purkinje neurons". The specification states:

> Purkinje cells play vital roles in maintaining balance and regulating movement. A loss of Purkinje cells results in deficits in these functions in several disorders: ataxia-telangiectasia, the most common cause of progressive ataxia in infancy; Menkes' Kinky Hair syndrome; the alcoholic cerebellar degenerations, particularly Wernicke-Korsakoff syndrome; and various prion diseases including scrapie, Creutzfeldt-Jakob, and Kuru.

Apparently, a loss of Purkinje cells results in deficits of their function in the listed disorders, but neither the specification nor the art of record teaches that a deficiency of Purkinje neuron is the cause of the aforementioned disorders. It was known in the art ataxia-telangiectasia is an inherited disease which affects many parts of the body; Menkes' disease is a X-linked recessive disorder; and Alcoholic cerebellar degeneration is most likely due to nutritional deficiencies, such as the vitamin deficiencies seen in Wernicke-Korsakoff's syndrome. The pathological changes of these disorders include the loss of Purkinje neurons. However, it was not known and the specification fails to teach that the recited disorders are caused by a deficiency of Purkinje neurons. Thus, the amendment is a departure from or an addition to the disclosure of the application as filed. Accordingly, it introduces new matter into the disclosure.

For reasons set forth above, the amendment filed 11/5/07 and 9/12/08 are objected to under 35 U.S.C. §132 because they introduce new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant **is required** to cancel the new matter in the reply to this Office Action.

Claims 8-13, 19-21, 34, 39, 41-45 stand and newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record and following.

The amended claim 34 recites "a disorder caused by a deficiency of Purkinje neurons". The specification states:

> Purkinje cells play vital roles in maintaining balance and regulating movement. A loss of Purkinje cells results in deficits in these functions in several disorders: ataxia-telangiectasia, the most common cause of progressive ataxia in infancy; Menkes' Kinky Hair syndrome; the alcoholic cerebellar degenerations, particularly Wernicke-Korsakoff syndrome; and various prion diseases including scrapie, Creutzfeldt-Jakob, and Kuru.

Given the broadest reasonable interpretation, instant claims are directed to treating disorders as listed above. However, the specification is completely silent with regard to the procedure, effects, and probability of the bone marrow mobilization therapy on the recited disorders, and whether any beneficial effect could be shown. For example, it was known in the art ataxia-telangiectasia is an inherited disease which affects many parts of the body; Menkes' disease is a X-linked recessive disorder; and Alcoholic cerebellar degeneration is most likely due to nutritional deficiencies, such as the vitamin deficiencies seen in Wernicke-Korsakoff's syndrome. The specification fails to provide an enabling disclosure showing that the bone marrow mobilization therapy could bring about any detectable beneficial effect on these diseases.

As to the Prion diseases including scrapie, CJD and Kuru, the current state of the art is such that "ALL ARE CURRENTLY **UNTREATABLE** AND ARE **ALWAYS FATAL**" (Wikipedia 2008). In fact, *Na et al*. (Neurosci Let 2009; 449:66-70) teaches scrapie-infection

induces neuron progenitor cells spontaneously undergoing neuron regeneration in mice brains. However, the neuron regeneration has not change the untreatable fate of the disease. *Vilette* (Vet Res 2008;Jul-Aug;39) teaches neuron progenitor cells are prone to scrapie multiplication (e.g. abstract and table I). As such it is highly unlikely the bone marrow mobilization therapy could bring any clinical beneficial effect for treating Prion diseases. The specification fails to shed lights on the hurdles known in the art, and fails to provide an enabling disclosure for what is now claimed.

In the remarks, the applicant first argues limitation from the specification may not be imported into the claims, and the claims are not directed to therapeutic uses per se. The applicant alleges that the examiner has improperly applied the standard of enablement to a claim not before the examiner.

In response, the MPEP 2111 instructs, "DURING PATENT EXAMINATION, THE PENDING CLAIMS MUST BE "GIVEN THEIR BROADEST REASONABLE INTERPRETATION CONSISTENT WITH THE SPECIFICATION." >THE FEDERAL CIRCUIT'S EN BANC DECISION IN PHILLIPS V. AWH CORP., 415 F.3D 1303, 75 USPQ2D 1321 (FED. CIR. 2005) EXPRESSLY RECOGNIZED THAT THE USPTO EMPLOYS THE "BROADEST REASONABLE INTERPRETATION" STANDARD:

> THE PATENT AND TRADEMARK OFFICE ("PTO") DETERMINES THE SCOPE OF CLAIMS IN PATENT APPLICATIONS NOT SOLELY ON THE BASIS OF THE CLAIM LANGUAGE, BUT UPON GIVING CLAIMS THEIR BROADEST REASONABLE CONSTRUCTION "IN LIGHT OF THE SPECIFICATION AS IT WOULD BE INTERPRETED BY ONE OF ORDINARY SKILL IN THE ART." IN RE AM. ACAD. OF SCI. TECH. CTR., 367 F.3D 1359, 1364[, 70 USPQ2D 1827] (FED. CIR. 2004).".

As such, when the claims recite "*administering an agent that mobilizes bone marrow cells to an individual having a disorder caused by a deficiency of Purkinje*

neurons", the intended use is apparent in light of the specification, and the standard applied to evaluate instant claims is therefore rightfully appropriate.

The applicant then argues only one use need be enabled, such as research in an experimental setting showing the formation in mice of bone marrow-derived cell/Purkinje neuron heterokaryons.

In response, as indicated previously the specification fails to show that administering an agent that mobilizes bone marrow cells would lead to the formation of the Purkinje/bone marrow-derived heterokaryon in the nervous system of the individual either in a clinical setting or an experimental setting. The specification only prophetically asserts that such is possible. The specification teaches that the inventors found that bone marrow-derived cells are capable of entering the nervous system and forming bone marrow derived neurons, particularly Purkinje neurons, and then contemplates using such approach for regeneration of neurons and treating neuronal disorders. The specification prophetically states that these diseases could be treated with a bone marrow cell mobilization treatment (paragraph 0089), and refers to prior art for details of the treatment citing *Chao et al*, (Blood, 1993), who administered G-CSF to "mobilize" macrophages and platelets for promoting bone marrow recovery from high dose chemotherapy. However, *Chao et al* use G-CSF in a completely different circumstance for achieving different goals, where patients underwent chemotherapy and administering growth factor G-CSF promoted regeneration of new blood cells. *Chao* reference does not provide any teaching regarding any changes in the nervous system of a subject, and thus the cited reference cannot substitute a specific guidance for

practicing instantly claimed invention. **The specification fails to provide any evidence that administering G-CSF, or any agent to that matter, would induce the formation of new Purkinje neuron in the nerve system, the specification fails to provide any evidence there are new formation of Purkinje neuron/BMC heterokaryon brought about by administering G-CSF**. Hence, the specification fails to provide an enabling disclosure for instantly claimed invention, and fails to provide an enabling disclosure for at least one use as they so asserted.

The applicant then argues that the working examples are not necessary to meet the enablement standard.

In response, MPEP 2164.02 states, "THE SPECIFICATION NEED NOT CONTAIN AN EXAMPLE IF THE INVENTION IS OTHERWISE DISCLOSED IN SUCH MANNER THAT ONE SKILLED IN THE ART WILL BE ABLE TO PRACTICE IT WITHOUT AN UNDUE AMOUNT OF EXPERIMENTATION. IN RE BORKOWSKI, 422 F.2D 904, 908, 164 USPQ 642, 645 (CCPA1970). LACK OF A WORKING EXAMPLE, HOWEVER, IS **A FACTOR** TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART". "IF LITTLE IS KNOWN IN THE PRIOR ART ABOUT THE NATURE OF THE INVENTION AND THE ART IS UNPREDICTABLE, THE SPECIFICATION WOULD NEED MORE DETAIL AS TO HOW TO MAKE AND USE THE INVENTION IN ORDER TO BE ENABLING". In the instant case, using bone marrow cell mobilization therapy to promote formation of Purkinje/BMC heterokaryon and to treat neuronal deficiency is a novel concept presented by instant applicant, little was known in the art about whether this idea was feasible, and the state of the art was such that there was no known means sufficient for producing a Purkinje/bone marrow-derived heterokaryon in an individual, in fact even references cited by the applicant pointed to evidence to the contrary such as the publication of

ZohInhofer (JAMA 2006), and hence it is upon the applicant to provide an enabling disclosure to guide the practice of instantly claimed invention at the time of instant filing date.

To this end, the specification fails to describe any specific agent or condition under which and using such agent the bone marrow cell mobilization therapy can be carried out to assert a neurological benefit, and it fails to teach what kind of effect in the brain tissue one is to expect upon the stem cell mobilization. Although the specification briefly mentioned bone mobilization therapy was known in the art, the art uses such therapy for a completely different purpose. Given the knowledge in the art as taught by *Garcia* (Neurotox Res 2000;2:115-37) and *Larkfors* (J Neurochem 1996;66:1362-73), given the specification is completely silent with regard to addressing or overcoming the art known hurdles, the prophetic teaching of the specification fails to provide an enabling disclosure for what is now claimed.

Further, from the teaching of the skilled as taught by *Garcia*, the state of the art is such in the context of neuronal degenerative disease model and human disease, there was a lack of relevance between the pathogenesis of the experimental lesion and corresponding neurodegenerative disorder; there was poor correlation between results obtained in acute, self-limited, selective deficit produced to experimental animals and those available in more complex, chronic and progressive disorders involving patients, and there was inadequate delivery of the active product to the target area in the human brain, and there was poor information from acute experiments in animals which does not predict long-term effects of chronic infusion in humans. In view of such state of the

art, and the disclosure provided by the applicant, instant claims remain in the realm of speculation.

The applicant then alleges that the Office missed the point and has not rebutted his argument that both bone marrow transplantation and bone marrow mobilization agents are acceptable methods for increasing the number of mobilized bone marrow cells in the blood stream.

In response, the applicant is reminded that the claimed invention is not directed to a method of increasing the number of mobilized bone marrow cells. The claimed invention is directed to producing a Purkinje/BMC heterokaryon. As to the two approaches, the Office has repeatedly indicated that the specification fails to establish that the bone marrow mobilization therapy is sufficient to substitute bone marrow transplantation to the extent that produces a neurological benefit. The point here is the prior art of record uses the mobilization therapy to supplement bone marrow transplantation, not substitute the BMT. The Office communication clearly stated upon reviewing the publications submitted by the applicant:

> In summary, it is noted the two references using G-CSF mobilization for regeneration of another organ (heart) were published after instant filing date, and establish the method has **no** benefit on myocardial regeneration in humans.
>
> The remain references report G-CSF effect on circulating progenitor cells for obtaining high quality donor cells for transplantation, not for substituting bone marrow cells with the G-CSF mobilization therapy. Hence, these references do not particularly support the applicant's assertion. From the numerous art cited, there is yet one reference clearly set forth that G-CSF substitutes for direct injection of bone marrow cells as asserted by the applicant. To the contrary, the needs to prepare donor for BMT implicitly suggest G-CSF has not replaced the need of bone marrow transplantation.

> Applicant submitted declaration illustrating that the progeny of a single HSC can form heterokaryons with Purkinje neurons. The declaration clarifies the fact that no lethal irradiation is required for grafted bone marrow cells to navigate to the brain. However, this showing does not address that it is G-CSF that induces the formation of Purkinje/bone marrow-derived heterokaryon.

Clearly, the Office has rebutted the applicant's assertion. It is incumbent upon the applicant to provide an enabling disclosure within the specification to establish that bone marrow mobilization therapy is capable of substitute bone marrow transplantation for the benefit of neuronal regeneration. The specification fails to do so, and thus it fails to meet the statutory enablement requirement.

As to the distinction between the written description and enablement, they are clearly separate statues and hence separate bases of rejections. The reasoning on page 7 of the Office action mailed 4/9/08 was only one of the many reasons for the lack of enablement rejection, these reasons have been discussed in detail from pages 8 through 17. It was unfounded to accuse the Office making the rejection solely on the written description. On the other hand, it is appropriate in the instant case to make the enablement rejection based on the lack of written description because the specification fails to provide an adequate description for an agent that directly induces formation of the Purkije/bone marrow-derived heterokaryon in the nervous system of the individual, and hence it would have required undue experimentation for those intending to practice instantly claimed invention hunting for the claimed agents.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

It is noted the following art rejection applied because of the applicant's assertion, "since the applicant already demonstrated that injected bone marrow cells can nevigate the blood circulation and find their way to the CNS, there is no scientific reason to doubt that mobilized bone marrow cells can do the same".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34, 39, 41-45 are rejected under 35 U.S.C. 102(b) as being anticipated by *Nimgaonkar et al*. (Exp Hematol 1995;23:1633-41), as evidenced by *Conradi et al*. (Acta Neuropathol 1984;65:99-109).

Nimgaonkar teaches a method of treating Gaucher disease comprising a step of administering cytokine G-CSF (e.g. figure 1, step 1). Although not relied upon, *Conradi* teaches that there were loss of Purkinje neurons in patients with Gaucher disease (a disorder having loss of Purkinje neurons, see e.g. table 3).

Accordingly, *Nimgaonkar* anticipates instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-13, 19, 20, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Nimgaonkar et al*. (Exp Hematol 1995;23:1633-41), in view of *Conradi et al*. (Acta Neuropathol 1984;65:99-109), and *Martinez-Murillo et al*. (Neurosci 1993;52:587-93).

Nimgaonkar et al. (Exp Hematol 1995;23:1633-41) teaches administering G-CSF to patients with Gaucher disease, and *Conradi et al*. teaches that Gaucher disease is accompanied by Purkinje neuron cell loss (see e.g. table 3). *Nimgaonkar* does not particularly teach using NGF combined with G-CSF.

Martinez-Murilloet supplemented the deficiency by establishing it was well known in the art that NGF plays a role on Purkinje cell recovery after damage. *Martinez-Murilloet* teaches Purkinje cells respond to injury by increasing surface expression of the low-affinity nerve growth factor receptor, suggesting that increased level of NGF may be beneficial for purkinje cell recovery in adulthood (e.g. Figures and discussion).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Nimgaonkar* in view of *Conradi,* by including a nerve growth factor in the treatment regimen as suggested by *Martinez-Murillo* with a reasonable expectation of success. The ordinary skilled artisan

would have been motivated to modify the claimed invention because the benefit for neuron protection. As to the means and timing of administering the two agents, they fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 19-21, 34, 39, 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Sanchez-Ramos et al*. (WO 99/56759), in view of *Bodine et al.* (Blood 1994;84:1482-91, IDS) and *Eglitis et al*. (USP 7,022,321).

Sanchez-Ramos teaches bone marrow cells are source of neurons for brain and spinal cord repair. *Sanchez-Ramos* transplanted bone marrow cells into rat brain at striatum, wherein the bone marrow cells did not remain localized to the site of the graft, but migrate throughout the brain and integrated into specific brain regions. *Sanchez-Ramos et al* teaches the most orderly integration of bone marrow cells was in the laminar distribution of cerebella Purkinje cells, where the bone marrow derived cells took on the Purkinje neuron phenotype (see e.g. the abstract, examples 2, 7, 8). *Sanchez-Ramos* does not teach using bone marrow mobilization in place of bone marrow cell transplantation.

Bodine supplements *Sanchez-Ramos* by establishing that bone marrow cell mobilization therapies were widely practiced in the art at the time of the instant priority date, and it was widely known that such therapies result in the movement of bone marrow cells from the bone marrow into the circulation (as asserted by the applicant). *Bodine* found that G-CSF increased peripheral blood pluripotent stem cells by three fold

in normal rats and 250-fold in splenectomized rats. *Bodine* reviews the state of the art has seen the capability of mobilized stem cells in hemotopoietic recovery, and suggest that mobilized peripheral progenitor cells may be the alternative to bone marrow cells in clinical therapy (e.g. column 2, page 1482).

Eglitis supplements *Sanchez-Ramos* in view of *Bodine* by establishing it was known in the art that intravenous injection of bone marrow progenitor cells would cross blood-brain barrier to arrive in the brain (e.g. the abstract, and example 5).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Sanchez-Ramos*, by using G-CSF mobilization in place of bone marrow transplantation as taught by *Bodine* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the mobilization therapy does not require a bone marrow donor and the transplantation procedure. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Sanchez-Ramos et al*. (WO 99/56759), in view of *Bodine et al.* (Blood 1994;84:1482-91, IDS) and *Eglitis et al*. (USP 7,022,321), as applied to claims 19-21, 34, 39, 41-45 above, further in view of *Martinez-Murillo et al*. (Neurosci 1993;52:587-93).

The combined teaching *supra* does not teach combining the G-CSF mobilization with a neuronal factor.

Martinez-Murillo supplemented the deficiency by establishing it was well known in the art that NGF plays a role on Purkinje cell recovery after damage. *Martinez-Murilloet* teaches Purkinje cells respond to injury by increasing surface expression of the low-affinity nerve growth factor receptor, suggesting that increased level of NGF may be beneficial for purkinje cell recovery in adulthood (e.g. Figures and discussion).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Sanchez-Ramos,* in view of *Bodine* and *Eglitis*, by including a nerve growth factor as taught by *Martinez-Murillo* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the benefit for neuron protection. As to the means and timing of administering of the two agents, they fall within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant first argue in a 2000 publication, *Sanchez-Ramos* disclaim the very same in vivo data that is presented in Example 3 of the cited publication.

The argument has been fully considered but found not persuasive. This is because the cited publication calls for caution using X-gal as a marker for neural transplantation studies. In the publication, *Sanchez-Ramos* illustrated how an insufficiently scrutinized X-gal positivity can be a pitfall in cell transplantation studies,

and provides recommendations for optimizing the specificity and reliability of the technique. *Sanchez-Ramos* analyzes his study as one of the examples, but does not negate the overall truth of his study. *Sanchez-Ramos* concludes, "DESPITE ITS PITFALLS, THE X-GAL HISTOCHEMICAL REATION HAS SO MANY SIGNIFICANT ADVANTAGES THAT IT SHOULD NOT BE SIMPLY JETTISONED FROM THE STOCKPILE OF TECHNIQUES USED BY THE NEURAL TRANSPLANT BIOLOGIST FOR EXAMINING ENGRAFTED TISSUE" (last paragraph, page 663).

The applicant then argues even if one skilled in the art had taken the '959 experiments at face value, that person would still not expect to see the formation of a Purkinje/bone marrow-derived heterokaryon as instantly claimed.

The argument has been fully considered but found not persuasive. This is because the preamble of claim 34 states an intended use of the process, and claims 39, 41-44 describe an intrinsic effect upon administering G-CSF to patients having a disorder of Purkinje neuron deficiency, and hence even though this and other references do not teach the effect, it would occur upon administering G-CSF to a subject.

Further, please note that intended use limitations bear little weight on the determination of novelty of the invention. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result

in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Accordingly, for reasons of record and set forth *supra*, the rejections stand.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI, M.D.** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633

QJL
December 15, 2008

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